CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074673

Trade Name : GUANFACINE TABLETS

Generic Name: Guanfacine Tablets USP

Sponsor : Amide Pharmaceutical, Inc.

Approval Date: February 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074673

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074673

APPROVAL LETTER

ANDA 74-673

FEB 28 1997

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated May 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Guanfacine Tablets USP, 1 mg and 2 mg.

Reference is also made to your amendments dated February 28, June 4, and December 11, 1996, and February 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Guanfacine Tablets USP, 1 mg and 2 mg, to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Tenex® Tablets, 1 mg and 2 mg, respectively, of A.H. Robins Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 2/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074673

FINAL PRINTED LABELING

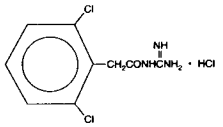
GUANFACINE TABLETS USP

7794-00

DESCRIPTION:

Guanfacine tablet is a centrally acting antihypertensive with α_2-adrenoceptor agonist properties in tablet form for oral administration.

The chemical name is N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride and its molecular weight is 282.56. Its structural formula is:



Guanfacine hydrochloride is a white to off-white powder; sparingly soluble in water and alcohol and slightly soluble in acetone.

Each tablet, for oral administration, contains guanfacine hydrochloride equivalent to 1 mg or 2 mg guanfacine. In addition, each tablet contains the following inactive ingredients:

1 mg - Anhydrous lactose, microcrystalline cellulose, pregelatinized starch, magnesium stearate and talc.

2 mg - Anhydrous lactose, microcrystalline cellulose, D&C yellow #10 aluminum lake, pregelatinized starch, magnesium stearate and talc.

CLINICAL PHARMACOLOGY:

Guanfacine hydrochloride is an orally active antihypertensive agent whose principal mechanism of action appears to be stimulation of central α_2-adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

The dose-response relationship for blood pressure and adverse effects of guanfacine given once a day as monotherapy has been evaluated in patients with mild to moderate hypertension. In this study patients were randomized to placebo or to 0.5 mg, 1 mg, 2 mg, 3 mg, or 5 mg of guanfacine. Results are shown in the following table. A useful effect was not observed overall until doses of 2 mg were reached, although responses in white patients were seen at 1 mg; 24 hour effectiveness of 1 mg to 3 mg doses was documented using 24 hour ambulatory monitoring. While the 5 mg dose added an increment of effectiveness, it caused an unacceptable increase in adverse reactions.

Mean Changes (mm Hg) from Baseline in Seated Systolic and Diastolic Blood Pressure for Patients Completing 4 to 8 Weeks of Treatment with Guanfacine Monotherapy

Mean Change S/D* Seated	n = (range)	Placebo	0.5 mg	1 mg	2 mg	3 mg	5 mg
White Patients	11-30	-1/-5	-6/-8	-8/-9	-12/-11	-15/-12	-18/-16
Black Patients	8-28	-3/-5	0/-2	-3/-5	-7/-7	-8/-9	-19/-15

*S/D = Systolic/ diastolic blood pressure.

Controlled clinical trials in patients with mild to moderate hypertension who were receiving a thiazide-type diuretic have defined the dose-response relationship for blood pressure response and adverse reactions of guanfacine given at bedtime and have shown that the blood pressure response to guanfacine can persist for 24 hours after a single dose. In the 12-week placebo-controlled dose-response study, patients were randomized to placebo or to doses of 0.5, 1, 2, and 3 mg of guanfacine, in addition to 25 mg chlorthalidone, each given at bedtime. The observed mean changes from baseline, tabulated below, indicate the similarity of response for placebo and the 0.5 mg dose. Doses of 1, 2, and 3 mg resulted in decreased blood pressure in the sitting position with no real differences among the three doses. In the standing position there was some increase in response with dose.

Mean Decreases (mm Hg) in Seated and Standing Blood Pressure for Patients Treated with Guanfacine in Combination with Chlorthalidone

Mean Change	n =	Placebo 63	0.5 mg 63	1 mg 64	2 mg 58	3 mg 59
S/D* Seated		-5/-7	-5/-6	-14/-13	-12/-13	-16/-13
S/D* Standing		-3/-5	-5/-4	-11/-9	-9/-10	-15/-12

* S/D = Systolic/diastolic blood pressure

While most of the effectiveness of guanfacine in combination (and as monotherapy in the white patients) was present at 1 mg, adverse reactions at this dose were not clearly distinguishable from those associated with placebo. Adverse reactions were clearly present at 2 and 3 mg (see Adverse Reactions).

In a second 12-week placebo-controlled study of 1, 2, or 3 mg of Guanfacine tablets administered with 25 mg chlorthalidone once daily, a significant decrease in blood pressure was maintained for a full 24 hours after dosing. While there was no significant difference between the 12 and 24 hour blood pressure reading, the fall in blood pressure at 24 hours was numerically smaller suggesting possible escape of blood pressure in some patients and the need for individualization of therapy.

In a double-blind, randomized trial, either guanfacine or clonidine was given at recommended doses with 25 mg chlorthalidone for 24 weeks and then abruptly discontinued. Results showed equal degrees of blood pressure reduction with the two drugs and there was no tendency for blood pressures to increase despite maintenance of the same daily dose of the two drugs. Signs and symptoms of rebound phenomena were infrequent upon discontinuation of either drug. Abrupt withdrawal of clonidine produced a rapid return of diastolic and especially, systolic blood pressure to approximately pre-treatment levels, with occasional values significantly greater than baseline, whereas guanfacine withdrawal produced a more gradual increase to pre-treatment levels, but also with occasional values significantly greater than baseline.

Pharmacodynamics: Hemodynamic studies in man showed that the decrease in blood pressure observed after single-dose or long-term oral treatment with guanfacine was accompanied by a significant decrease in peripheral resistance and a slight reduction in heart rate (5 beats/min). Cardiac output under conditions of rest or exercise was not altered by guanfacine.

Guanfacine lowered elevated plasma renin activity and plasma catecholamine levels in hypertensive patients, but this does not correlate with individual blood-pressure responses.

Growth hormone secretion was stimulated with single oral doses of 2 and 4 mg of guanfacine. Long-term use of guanfacine had no effect on growth hormone levels.

Guanfacine had no effect on plasma aldosterone. A slight but insignificant decrease in plasma volume occurred after one month of guanfacine therapy. There were no changes in mean body weight or electrolytes.

Pharmacokinetics: Relative to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours with an average of 2.6 hours after single oral doses or at steady state.

The area under the concentration-time curve (AUC) increases linearly with the dose.

In individuals with normal renal function, the average elimination half-life is approximately 17 hr (range 10-30 hr). Younger patients tend to have shorter elimination half-lives (13-14 hr) while older patients tend to have half-lives at the upper end of the range. Steady state blood levels were attained within 4 days in most subjects.

In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.

The guanfacine-to-creatinine clearance ratio is greater than 1.0, which would suggest that tubular secretion of drug occurs.

The drug is approximately 70% bound to plasma proteins, independent of drug concentration.

The whole body volume of distribution is high (a mean of 6.3L/kg), which suggests a high distribution of drug to the tissues.

The clearance of guanfacine in patients with varying degrees of renal insufficiency is reduced, but plasma levels of drug are only slightly increased compared to patients with normal renal function. When prescribing for patients with renal impairment, the low end of the dosing range should be used. Patients on dialysis also can be given usual doses of guanfacine hydrochloride as the drug is poorly dialyzed.

INDICATIONS AND USAGE:

Guanfacine tablets are indicated in the management of hypertension. Guanfacine tablets may be given alone or in combination with other antihypertensive agents, especially-thiazide type diuretics.

CONTRAINDICATIONS:

Guanfacine hydrochloride is contraindicated with known hypersensitivity to guanfacine hydrochloride.

PRECAUTIONS:

General. Like other antihypertensive agents, Guanfacine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal or hepatic failure.

Sedation. Guanfacine, like other orally active central α_2-adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When guanfacine is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central α_2-adrenergic agonists may be associated with increases(from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive guanfacine should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trails, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with guanfacine.

Drug Interactions. The potential for increased sedation when Guanfacine is given with other CNS-depressant drugs should be appreciated.

The administration of guanfacine concomitantly with a known microsomal enzyme inducer (phenobarbital or phenytoin) to two patients with renal impairment reportedly resulted in significant reductions in elimination half-life and plasma concentration. In such cases, therefore, more frequent dosing may be required to achieve or maintain the desired hypotensive response. Further, if guanfacine is to be discontinued in such patients, careful tapering of the dosage may be necessary in order to avoid rebound phenomena (see *Rebound* above).

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1-2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Guanfacine was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of guanfacine have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models, guanfacine was not mutagenic.
No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and to rabbits at 20 times the maximum recommended human dose resulted in no evidence of harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Guanfacine is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Guanfacine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Guanfacine is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in pediatric patients under 12 years of age have not been demonstrated. Therefore, the use of Guanfacine in this age group is not recommended.

ADVERSE REACTIONS:

Adverse reactions noted with guanfacine are similar to those of other drugs of the central α_2-adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia) dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases; although clear cause and effect relationships to Guanfacine could not be established, should a rash occur, Guanfacine should be discontinued and the patient monitored appropriately.

In the dose-response monotherapy study described under Clinical Pharmacology, the frequency of the most observed adverse reaction showed a dose relationship from 0.5 to 3 mg as follows:

Adverse Reaction	Placebo n = 59	0.5 mg n = 60	1 mg n = 61	2 mg n = 60	3 mg n =59
Dry Mouth	0%	10%	10%	42%	54%
Somnolence	8%	5%	10%	13%	39%
Asthenia	0%	2%	3%	7%	3%
Dizziness	8%	12%	2%	8%	15%
Headache	8%	13%	7%	5%	3%
Impotence	0%	0%	0%	7%	3%
Constipation	0%	2%	0%	5%	15%
Fatigue	2%	2%	5%	8%	10%

The percent of patients who dropped out because of adverse reactions are shown below for each dosage group.

	Placebo	0.5 mg	1 mg	2 mg	3 mg
Percent dropouts	0%	2.0%	5.0%	13%	32%

The most common reason for dropouts among patients who received guanfacine were dry mouth, somnolence, dizziness, fatigue, weakness and constipation.
In the 12-week, placebo-controlled, dose-response study of guanfacine administered with 25 mg chlorthalidone at bedtime, the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg as follows:

Adverse Reaction	Placebo n = 73	0.5 mg n = 72	1 mg n =72	2 mg n = 72	3 mg n =72
Dry Mouth	5(7%)	4(5%)	6(8%)	8(11%)	20(28%)
Somnolence	1(1%)	3(4%)	0(0%)	1(1%)	10(14%)
Asthenia	0(0%)	2(3%)	0(0%)	2(2%)	7(10%)
Dizziness	2(2%)	1(1%)	3(4%)	6(8%)	3(4%)
Headache	3(4%)	4(3%)	3(4%)	1(1%)	2(2%)
Impotence	1(1%)	1(0%)	0(0%)	1(1%)	3(4%)
Constipation	0(0%)	0(0%)	0(0%)	1(1%)	1(1%)
Fatigue	3(3%)	2(3%)	2(3%)	5(6%)	3(4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who dropped out and the dose at which the dropout occurred were as follows:

Dose	Placebo	0.5 mg	1 mg	2 mg	3 mg
Percent dropouts	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second 12-week placebo-controlled combination therapy study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth, 47%; constipation, 16%; fatigue, 12%; somnolence, 10%; asthenia, 6%; dizziness, 6%; headache, 4%; and insomnia, 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.
In the clonidine-guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were as follows:

Adverse Reaction	Guanfacine (n = 279)	Clonidine (n = 278)
Dry Mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials of Guanfacine with a diuretic were:

Cardiovascular - bradycardia, palpitations, substernal pain
Gastrointestinal - abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS - amnesia, confusion, depression, insomnia, libido decrease
ENT disorders - rhinitis, taste perversion, tinnitus
Eye disorders - conjunctivitis, iritis, vision disturbance
Musculoskeletal - leg cramps, hypokinesia
Respiratory - dyspnea
Dermatologic - dermatitis, pruritus, purpura, sweating
Urogenital - testicular disorder, urinary incontinence
Other - malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reaction at any time **during the study**	Incidence of adverse reactions at end of **one year**
	n = 580	**n = 580**
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n=20), weakness (n=12), constipation (n=7), somnolence (n=3), nausea (n=3), orthostatic hypotension (n=2), insomnia (n=1), rash (n=1), nightmares (n=1), headache (n=1), and depression (n=1).

Postmarketing Experience. An open-label postmarketing study involving 21,718 patients was conducted to assess the safety of Guanfacine tablets 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the postmarketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly Guanfacine-related events observed in the postmarketing study and/or reported spontaneously include:

BODY AS A WHOLE	asthenia, chest pain, edema, malaise, tremor
CARDIOVASCULAR	bradycardia, palpitations, syncope, tachycardia
CENTRAL NERVOUS SYSTEM	paresthesias, vertigo
EYE DISORDERS	blurred vision
GASTROINTESTINAL SYSTEM	abdominal pain, constipation, diarrhea, dyspepsia
LIVER AND BILIARY SYSTEM	abnormal liver function tests
MUSCULO-SKELETAL SYSTEM	arthralgia, leg cramps, leg pain, myalgia
PSYCHIATRIC	agitation, anxiety, confusion, depression, insomnia, nervousness
REPRODUCTIVE SYSTEM, MALE	impotence
RESPIRATORY SYSTEM	dyspnea
SKIN AND APPENDAGES	alopecia, dermatitis, exfoliative dermatitis, pruritus rash
SPECIAL SENSES	alterations in taste
URINARY SYSTEM	nocturia, urinary frequency

Rare, serious disorders with no definitive cause and effect relationship to Guanfacine have been reported spontaneously and/or in the postmarketing study. These events include acute renal failure, cardiac fibrillation, cerebrovascular accident, congestive heart failure, heart block, and myocardial infarction.

DRUG ABUSE AND DEPENDENCE:

No reported abuse or dependence has been associated with the administration of Guanfacine.

OVERDOSAGE:

Signs and Symptoms. Drowsiness, lethargy, bradycardia and hypotension have been observed following overdose with guanfacine.

A 25-year-old female intentionally ingested 60 mg. She presented with severe drowsiness and bradycardia of 45 beats/minute. Gastric lavage was performed and an infusion of isoproterenol (0.8 mg in 12 hours) was administered. She recovered quickly and without sequelae.

A 28-year-old female who ingested 30-40 mg developed only lethargy, was treated with activated charcoal and a cathartic, was monitored for 24 hours, and was discharged in good health.

A 2-year-old male weighing 12 kg, who ingested up to 4 mg of guanfacine, developed lethargy. Gastric lavage (followed by activated charcoal and sorbitol slurry via NG tube) removed some tablet fragments within 2 hours after ingestion, and vital signs were normal. During 24-hour observation in ICU, systolic pressure was 58 and heart rate 70 at 16 hours post-ingestion. No intervention was required, and child was discharged fully recovered the next day.

Treatment of Overdosage. Gastric lavage and supportive therapy as appropriate Guanfacine is not dialyzable in clinically significant amounts (2.4%).

DOSAGE AND ADMINISTRATION:

The recommended initial dose of Guanfacine tablets when given alone or in combination with another antihypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, a dose of 2 mg may be given, although most of the effect of Guanfacine is seen at 1 mg (see Clinical Pharmacology). Higher daily doses have been used, but adverse reactions increase significantly with doses above 3 mg/day.

The frequency of rebound hypertension is low, but it can occur. When rebound occurs, it does so after 2-4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2-4 days) without ill effects.

HOW SUPPLIED:

Guanfacine tablets USP, are available as follows:

1 mg - White unscored round tablet debossed "A 1" on one side in bottles of 100 (NDC 52152-118-02) and 500 (NDC 52152-118-04).

2 mg - Yellow unscored round tablet debossed "A 2" on one side in bottles of 100 (NDC 52152-119-02) and 500 (NDC 52152-119-04).

Store at controlled room temperature, between 15°C and 30°C (59°F and 86°F)

Dispense in tight, light-resistant container as defined in the USP.

12/96

MANUFACTURED BY
AMIDE PHARMACEUTICAL, INC.
LITTLE FALLS, NJ 07424

AMIDE

NDC 52152-118-02

GUANFACINE TABLETS USP

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Guanfacine hydrochloride
Equivalent to 1 mg guanfacine

USUAL DOSAGE: For dosage and other prescribing information, see accompanying product literature.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7795-00

N 3 52152-118-02 8

Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

AMIDE

NDC 52152-118-04

GUANFACINE TABLETS USP

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:
Guanfacine hydrochloride
Equivalent to 1 mg guanfacine

USUAL DOSAGE: For dosage and other prescribing information, see accompanying product literature.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7796-00

N 3 52152-118-04 2

Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

AMIDE

NDC 52152-119-02

GUANFACINE TABLETS USP 2 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

EACH TABLET CONTAINS:
Guanfacine hydrochloride
Equivalent to 2 mg guanfacine

USUAL DOSAGE: For dosage and other prescribing information, see accompanying product literature.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7797-00

N 3 52152-119-02 5

Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

AMIDE

NDC 52152-119-04

GUANFACINE TABLETS USP 2 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

EACH TABLET CONTAINS:
Guanfacine hydrochloride
Equivalent to 2 mg guanfacine

USUAL DOSAGE: For dosage and other prescribing information, see accompanying product literature.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7798-00

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Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074673

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-673

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 E. Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
Tenex® Tablets, 1 mg/tablet
Tenex® Tablets, 2 mg/tablet
A.H. Robins Company
1407 Cummins Drive
Richmond, VA 23220

All patents have expired for the drug substance.

The firm has acknowledged the Exclusivity Code I-91, expiration date May 11, 1996 and has certified that they are not infringing with the exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Guanfacine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

5/16/95	Original submission.
6/27/95	Response to Agency's letter of 6/2/95.
7/5/95	New Correspondence - Revision to 306(k) certification and labeling comparison.
7/27/95	Amendment - Addition of 1 mg tablet.
2/28/96	Amendment - Response to Bioequivalence letter of 2/7/96.
5/8/96	Response to Agency's letter of 3/12/96.
6/4/96	Response to Telephone Request by Bioequivalence, 6/4/96.
12/11/96	**Response to Agency's letter of 12/5/96.**
2/12/97	**Telephone Amendment, Corrected 2/13/97.**

FDA:

6/2/95	Refuse to File letter issued.
7/14/95	Receipt Acknowledged, acceptable for filing, 6/29/95.
2/7/96	Issuance of Bioequivalence Request for Information letter.
3/12/96	Issuance of Not Approvable letter.
6/10/96	Issuance of Bioequivalence No Further Questions letter.
12/5/96	Issuance of Not Approvable letter.
2/11/97	Telephone request for Minor Revision.

10. PHARMACOLOGICAL CATEGORY
Central Alpha-2 Agonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

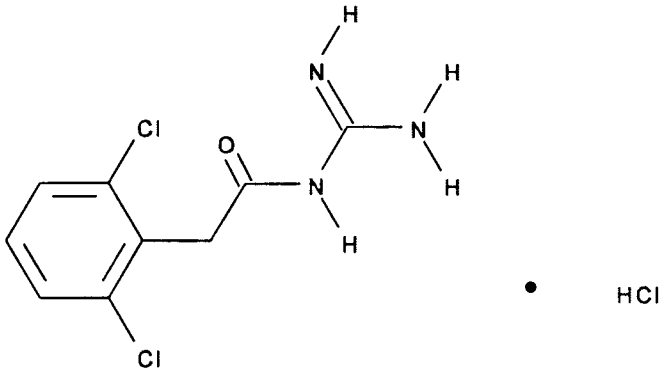
13. DOSAGE FORM
Tablet for oral administration

14. POTENCY
1 mg/tablet
2 mg/tablet

15. CHEMICAL NAME AND STRUCTURE

Guanfacine Hydrochloride

$C_9H_9Cl_2N_3O.HCl$; M.W. = 282.56



N-Amidino-2-(2,6-dichlorophenyl)acetamide monohydrochloride.
CAS [29110-48-3]

Innovator Insert: Guanfacine HCl is a white to off-white powder, sparingly soluble in water and alcohol and slightly soluble in acetone.

Merck: White needles, mp 213 - 216°C. LD_{50} in mice 165 mg.kg orally.

16. RECORDS AND REPORTS
12/20/95 - Chemistry Review #1, G.J. Smith.
1/24/96 - Bioequivalence Review, H. Nguyen.
2/6/96 - Labeling Review, A. Vezza.
8/13/96 - Labeling Review, J. White.
11/18/96 - Labeling Review, J. White.
10/23/96 - Chemistry Review #2, G.J. Smith.
1/15/97 - Labeling Review, J. White.

17. COMMENTS
The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory, J. White, 1/15/97.

The Division of Bioequivalence found the drug product equivalent and granted waiver, H. Nguyen, 6/5/96 .

Acceptable EIR issued by the Office of Compliance, 6/17/96.

Methods validation not required since drug substance and drug product are compendial.

(b)4 - for drug substance was satisfactory, N. Gregory, 8/4/94.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: February 2, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074673

BIOEQUIVALENCE REVIEW(S)

D-2

ANDA 74-673

Amid Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 East Main Street
Little Falls NJ 07424

JUN 10 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Guanfacine Tablets 1 mg and 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 ml of deaerated water at 37°C using USP 23 apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 5 1996

Guanfacine HCl Tablets, 1 mg & 2 mg
ANDA # 74-673
Reviewer: Hoainhon Nguyen
WP # 74673a.296

Amide Pharmaceutical
Little Falls, NJ
Submission Date:
February 28, 1996
June 4, 1996

Review of a Study Amendment

The firm has submitted an amendment to the biostudy results in response to the Division of Bioequivalence's following Deficiency comments:

"1. Long term stability should be submitted to validate fully the biostudy data. Potency for the reference biolot should also be specified.

2. Individual plasma concentration and pharmacokinetic parameter data should also be submitted on a diskette."

In response to Deficiency comment No. 1 above, the firm has provided complete data for stability studies: 157-day long term stability study of guanfacine in plasma samples at -22°C; 23.1-hour short term stability study of guanfacine in plasma samples at 22°C; 3-cycle freeze-thaw stability study of guanfacine in plasma samples; 4.5-hour autosampler stability study of guanfacine in plasma samples at 22°C; 120-hour dry extract stability study of guanfacine; 24-hour wet extract stability study of guanfacine in methanol; 218-day stock solution stability study of guanfacine in methanol and 188-day stock solution stability study of the internal standard in methanol. The variation between stored and fresh Comparison samples in these stability studies was between 1 to 8%. The stability studies are acceptable.

Potency of the reference biolot (Tenex 2 mg tablets, Lot No. 0940758) and the test biolot (Lot No. 4293A) were 98.9% and 101.2%, respectively. (Faxed amendment dated June 4, 1996)

In response to Deficiency comment No. 2, a diskette of individual concentration and pharmacokinetic parameter data for the biostudy was submitted. Individual concentration data were spot-checked, ANOVA was run for lnAUCs and lnCMAX, and 90% confidence intervals for lnAUCs and lnCMAX were calculated. The results of the biostudy as presented by the firm were therefore verified.

Recommendations: (The recommendations are based on the review of submissions dated May 16, 1995, July 27, 1995 and February 28, 1996)

1. The single-dose, fasting bioequivalence study conducted by Amide Pharmaceutical on the test product, Guanfacine HCl Tablets, 2 mg, lot # 4293A, comparing it with the reference product, Tenex^{R} Tablets, 2 mg, lot # 0940758, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting conditions.

2. The in-vitro dissolution testing conducted by Amide Pharmaceutical on its Guanfacine HCl Tablets, 2 mg and 1 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of deaerated water at 37C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The firm has demonstrated that the formulation of its Guanfacine HCl Tablets, 1 mg, is proportionally similar to the 2 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 1 mg tablets is granted. The firm's Guanfacine HCl Tablets, 1 mg, is therefore deemed bioequivalent to Tenex^{R} Tablets, 1 mg, manufactured by A.H.Robins.

/S/ 6/4/96
Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 6/4/96

/S/

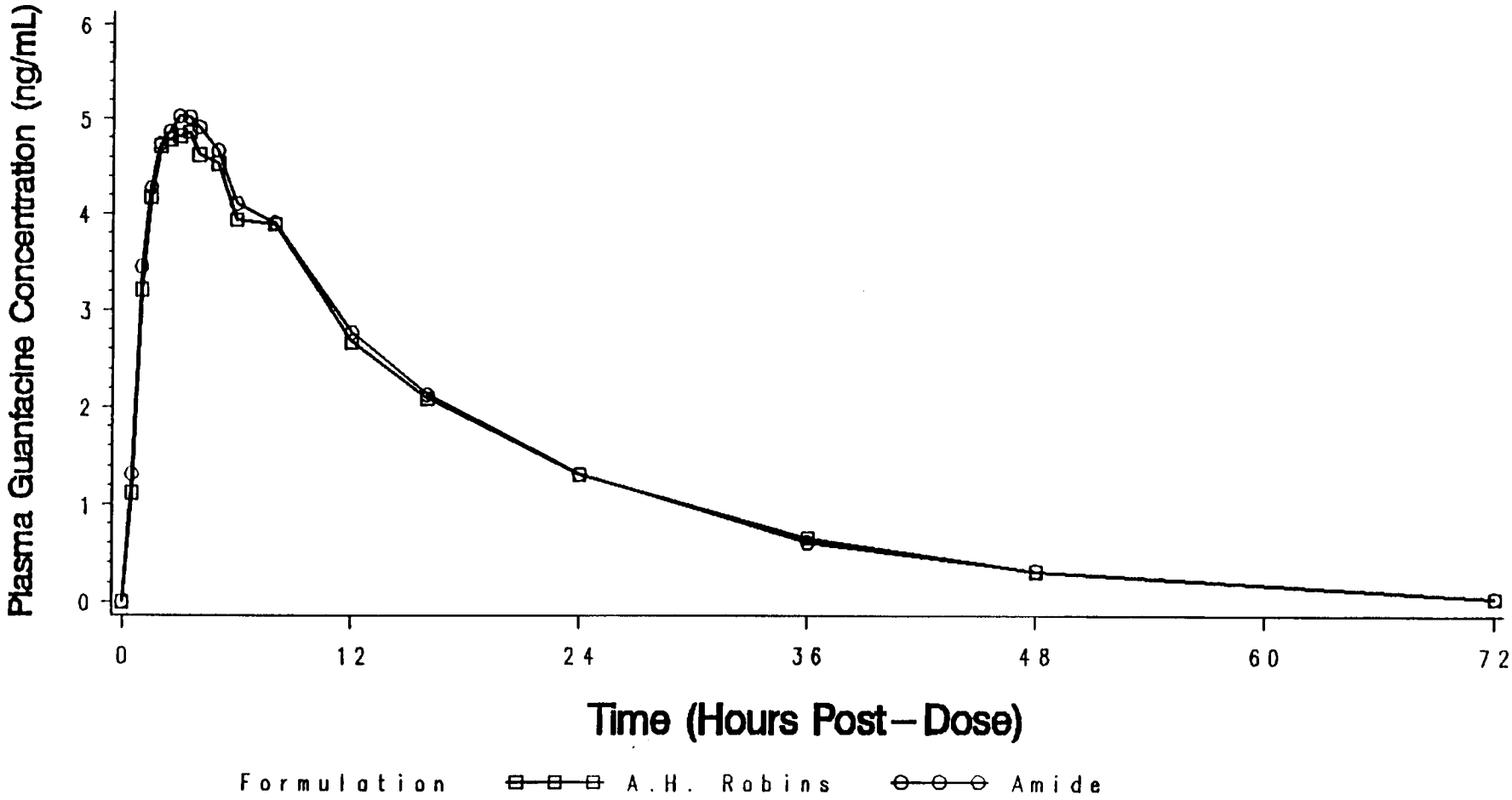
Concur: _____ Date: 6/5/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-673 (original, duplicate), HFD-630(OGD), HFD-600(Hare), HFD-652(Huang, Nguyen), HFD-344(CViswanathan), Drug File, Division File

Hnguyen/05-30-96/WP #74673a.296

Attachments: 2 pages

Figure 2
Project No. 940019
Mean Plasma Guanfacine Concentrations
(Linear Plot)



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Wp # 74673 a, 296 Attachment 1 of 2

(b)4 - Confidential Business

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NP # 74673 a .296 Attachment 2 of 2

AMIDE PHARMACEUTICAL, INC.

GUANFACINE TABLETS

FORMULATION COMPARISION FOR GUANFACINE TABLETS

EACH TABLET CONTAINS	GUANFACINE TABLETS 2 mg mg/tablet	GUANFACINE TABLETS 1 mg mg/tablet
Guanfacine Hydrochloride (Equivalent to 2 mg and 1 mg Guanfacine)	2.346 *	1.173
Lactose Anhydrous, NF	(b)4 - Confidential Business	
Microcrystalline Cellulose, NF		
D&C Yellow #10 Aluminum Lake		
Starch Pregelatinized, NF		
Magnesium Stearate, NF		
Talc, USP		
TOTAL WEIGHT:	125.00	125.0

* Contains 2% excess to compensate for moisture content and production losses.

NOTE: Bioequivalence study is performed on 2 mg strength only.

DIV

ANDA 74-673

FEB -7 1996

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls NJ 07424

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on May 16, 1995 and your amendments dated June 27, and July 27, 1995, for Guanfacine Tablets 1 mg and 2 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The long term stability study should be submitted to validate fully the bioequivalence study data. Potency for the reference bioequivalence lot should be specified.

2. The individual plasma concentration and pharmacokinetic parameter data should also be submitted on a diskette.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

[redacted].D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

JAN 24 1996

Guanfacine HCl Tablets, 1 mg & 2 mg
ANDA # 74-673
Reviewer: Hoainhon Nguyen
WP # 74673sdw.795

Amide Pharmaceutical
Little Falls, NJ
Submission Date:
May 16, 1995
July 27, 1995
June 27, 1995

Review of a Bioequivalence Study, Dissolution Data and a Waiver Request

I. Background:

Guanfacine is a centrally acting antihypertensive with alpha$_2$-adrenoceptor agonist properties, used in the management of hypertension alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The principal mechanism of action of guanfacine appears to be stimulation of central alpha$_2$-adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate. Guanfacine hydrochloride is sparingly soluble in water.

Relative to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours with an average of 2.6 hours after single oral dose or at steady state. The area under the concentration-time curve increases linearly with the dose.

The average elimination half-life in healthy individuals is approximately 17 hours (range 10-30 hours). Steady state blood levels were attained within 4 days in most subjects. Guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.

The drug is approximately 70% bound to plasma proteins, independent of drug concentration. The whole body volume of distribution is high (a mean of 6.3 L/kg), which suggests a high distribution of drug to the tissues.

Most common adverse effects of guanfacine HCl include dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence.

Guanfacine hydrochloride is available commercially as Tenex^{R} oral tablets, 1 mg and 2 mg, manufactured by A. H. Robins.

The firm has submitted the results of a fasting, single-dose bioequivalence study comparing its guanfacine HCl tablets, 2 mg, with Robins' Tenex^{R} 2 mg tablets. The firm has also requested a waiver of in vivo bioequivalence requirements for its guanfacine HCl 1 mg tablets based on in vitro dissolution data and formulation proportionality of the 1 mg to 2 mg strength.

Note: Currently, the Division of Bioequivalence does not require a food study for approval of guanfacine HC l tablet products.

II. Bioequivalence Study: (Protocol No. 940019)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Amide's guanfacine HCl tablets, 2 mg, and A.H.Robin's Tenex^{R} Tablets, 2 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at (b)4 - Confidential Business, between January 28, 1995 and February 14, 1995. The principal investigator was (b)4 - Plasma samples were assayed by (b)4 - Confidential (b)4 - under the supervision of (b)4 -., between February 19, 199 and March 06, 1995.

Demographics:

Twenty-six normal, healthy, non-tobacco using male volunteers between 18-45 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in the study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight range was 65.7 to 92.0 kilograms, and height range 165.1 to 193.0 cm.

Inclusion criteria:

Subjects especially did not have any history of: cardiovascular, pulmonary, hepatic, renal, hematologic, gastro-intestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease, alcoholism or drug abuse within the last year, hypersensitivity or an idiosyncratic reaction to guanfacine HCl or to other phenylacetyl-guanidine derivatives.

Restrictions:

They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed for at least 24 hours prior to days on which the subjects were dosed and throughout the confinement period of the study. The subjects fasted for 10 hours prior to and 4 hours after each drug administration. The washout duration between the two phases was fourteen days. Duration of confinement was 12 hours pre-dose to approximately 36 hours post-dose.

Treatments and Sampling:

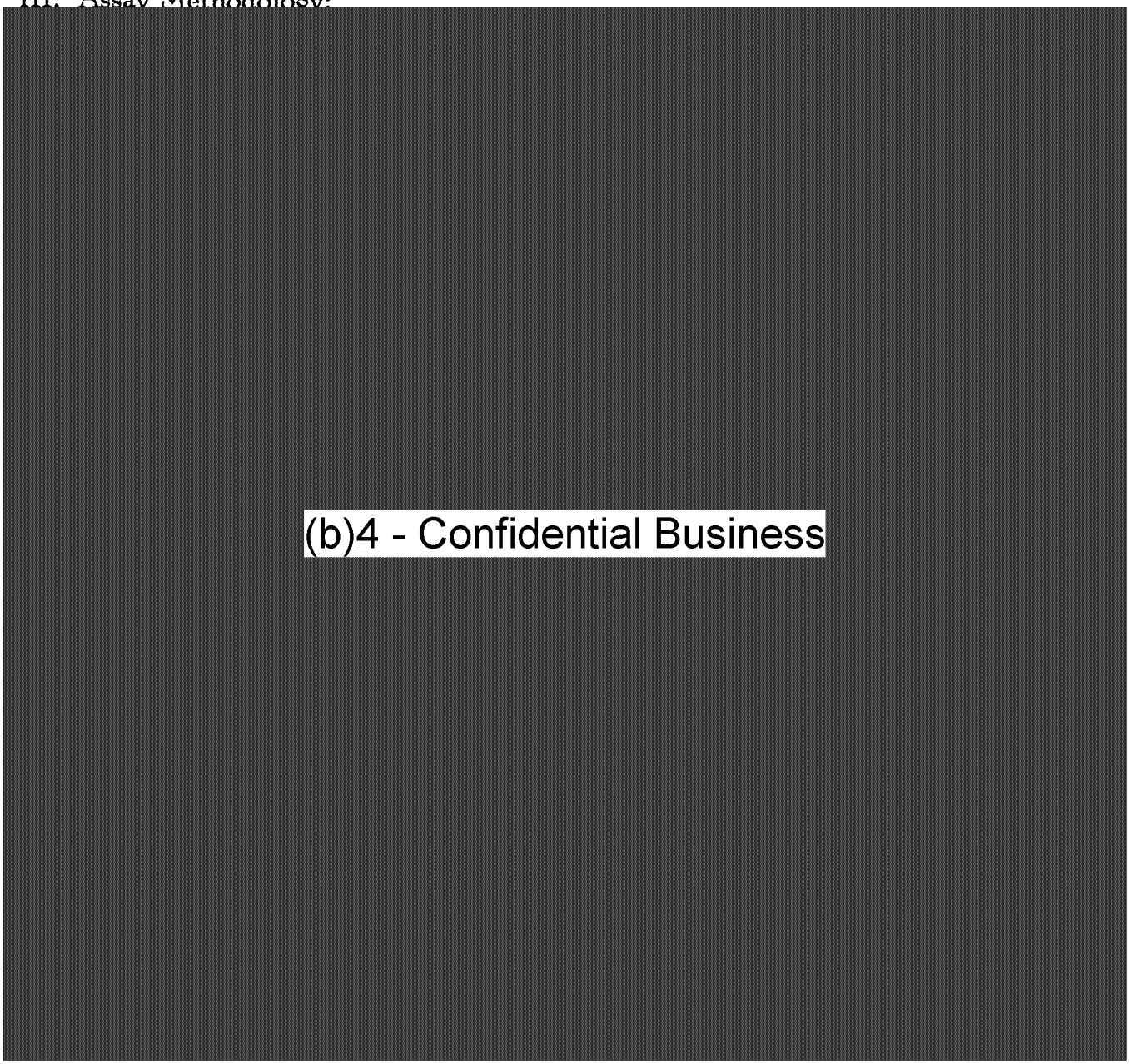
The two treatments consisted of a single 2 mg dose of either the test product or reference product taken orally with 240 ml of water.

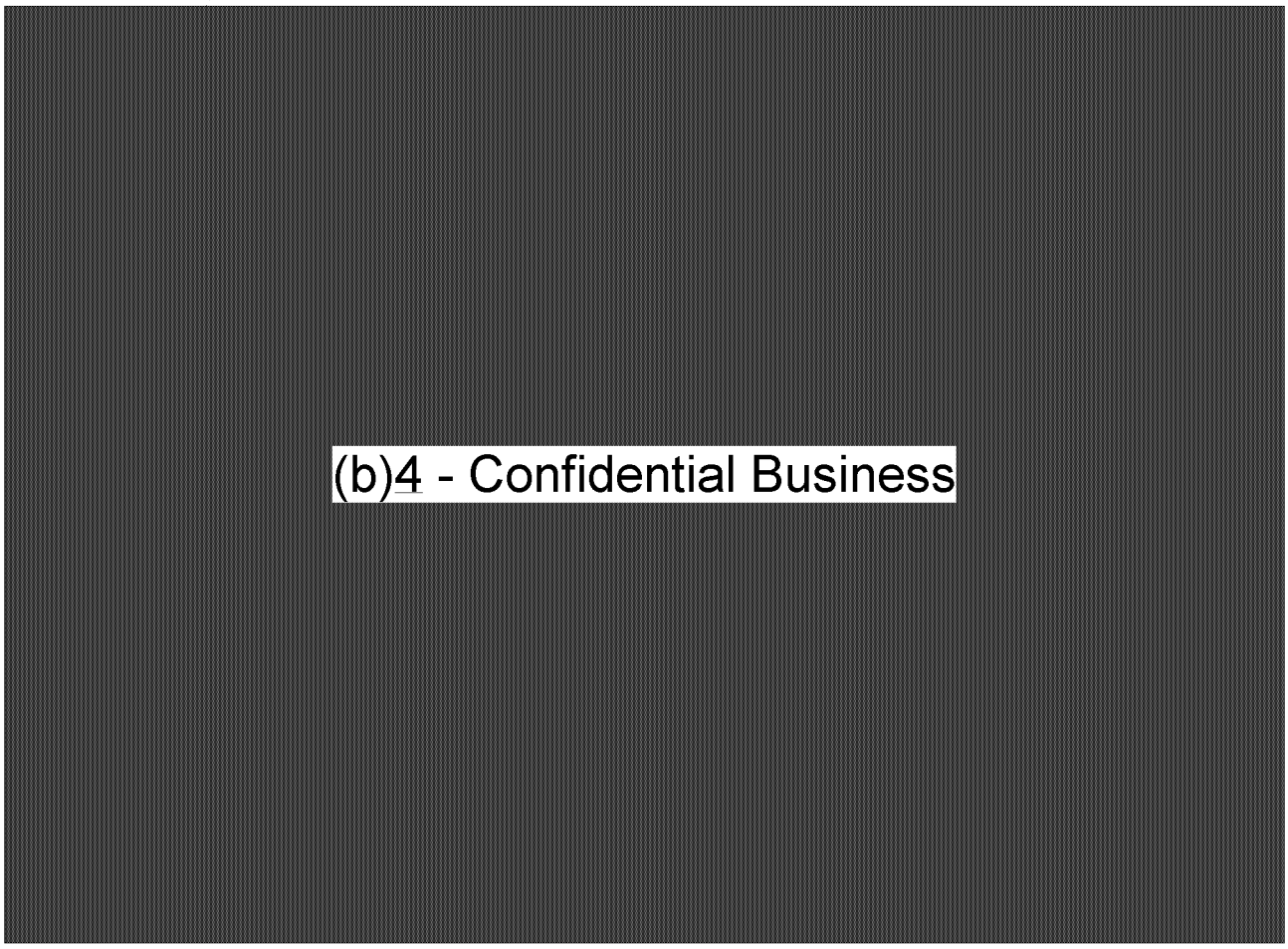
Test Product: Amide's Guanfacine HCl Tablets, 2 mg, lot # 4293A3 (Batch size of (b)4 - , potency of 101.8% (RSD=0.9%)).

Reference product: A.H. Robins' Tenex^{R} Tablets, 2 mg, lot # 0940758 (Potency not given).

Blood samples were collected at predose, 0.50, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20^{0}C until shipping to the analytical laboratory.

III. Assay Methodology:





IV. Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two one-sided t-tests.

Results:

All twenty-six of enrolled volunteers completed the clinical portion of the study. As per protocol, statistical analyses were performed using data from Subjects # 1-24.

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX, TMAX and THALF. There was a significant difference between treatments for KEL (p=0.0430). The results are summarized in the tables below:

Table I

Guanfacine Comparative Pharmacokinetic Parameters
Dose = 2 mg; n = 24

Parameters	Amide Mean (CV)	Tenex^{R} Mean (CV)	90% C.I.	% T/R
AUC (0-T) ng.hr/ml	86.80*	85.38*	[0.97;1.06]	101.7
AUC (0-Inf) ng.hr/ml	90.77*	89.69*	[0.96;1.06]	101.2
CMAX(ng/ml)	5.345*	5.198*	[0.98;1.08]	102.8
TMAX (hrs)	3.36(30)	3.15(39)		
KEL (1/hrs)	0.061(15)	0.059(13)		
T1/2 (hrs)	11.58(16)	11.88(14)		

*Least Squares geometric means

Table II
Comparative Mean Plasma Levels of Guanfacine
ng/ml(CV)
Dose = 2 mg; n = 24

Hour	Amide	Tenex[R]
0	0	0
0.50	1.315(92)	1.116(115)
1.00	3.451(45)	3.212(46)
1.50	4.273(29)	4.173(31)
2.00	4.733(29)	4.710(23)
2.50	4.864(20)	4.781(21)
3.00	5.026(19)	4.814(18)
3.50	5.016(16)	4.856(18)
4.00	4.910(17)	4.616(18)
5.00	4.663(19)	4.528(19)
6.00	4.109(20)	3.938(17)
8.00	3.905(21)	3.892(23)
12.00	2.773(21)	2.675(19)
16.00	2.128(25)	2.088(19)
24.00	1.318(27)	1.307(22)
36.00	0.612(36)	0.657(30)
48.00	0.320(60)	0.310(35)
72.00	0.044(200)	0.038(205)
AUC(0-T)ng.hr/ml	88.99(25)	87.15(21)
AUC(0-Inf)ng.hr/ml	92.99(24)	91.41(20)
CMAX	5.424(18)	5.306(21)

V. Adverse Effects:

There were 9 adverse events reported in 7 subjects. The drug-related events included dizziness, low heart rate and nausea. None of the adverse reactions was considered serious by the investigator.

VI. Dissolution Testing:

Drug (Generic Name): Guanfacine HCl Tablets Firm: Amide Pharm.
Dose Strength: 1 mg & 2 mg ANDA # 74-673
Submission Date: 07-27-95

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 50 No. Units Tested: 12

Medium: Water Volume: 900 ml

Reference Drug: (Manuf.) Tenex[R] Tablets; A.H.Robins

Assay Methodology: [redacted](b)4 -[redacted]

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Mean % Dissolved	Range	(CV)	Reference Product Mean % Dissolved	Range	(CV)
	Lot # 4293A			Lot # 0940758		
	Strength (mg) 2			Strength (mg) 2		
20	89.3	[redacted](b)4 -	(1.2%)	81.6	[redacted](b)4 -	(3.1%)
30	92.3	Confidentia	(2.0%)	85.6	Confidentia	(1.2%)
45	98.1	Business	(0.8%)	94.1	Business	(1.1%)
	Lot # 5073A			Lot # 0931217		
	Strength (mg) 1			Strength (mg) 1		
20	89.4	[redacted](b)4 -	(2.4%)	73.1	[redacted](b)4 -	(3.8 %)
30	91.3	Confidentia	(2.0%)	78.4	Confidentia	(1.4%)
45	96.2	Business	(2.0%)	82.0	Business	(5.2%)

Specifications: NLT [redacted](b)4n 45 min

VII. Formulation Proportionality:

Formulation of the 1 mg strength of the test product is proportionally similar to the 2 mg strength of the test product. See attachment.

VIII. Deficiencies:

1. Long term stability study should be submitted to validate fully the biostudy data. Potency for the reference biolot should also be specified.

2. Individual plasma concentration and pharmacokinetic parameter data should also be submitted on a diskette.

IX. Comment: (Not to be released by FOI)

The current dissolution specifications for guanfacine Hcl tablets are as stated in the Recommendation # 2 below. The specifications of "not less than (b)4 of the labeled amount of the drug in the dosage form to be dissolved in 30 minutes" as recommended for (b)4 - Confidential Business may not be appropriate for other products of guanfacine Hcl tablets, including the Reference Listed Drug Product, A.H.Robins' Tenex^R Tablets, as shown in the dissolution data of the 1 mg strength of the RLD in this ANDA.

X. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Amide Pharmaceutical on the test product, Guanfacine HCl Tablets, 2 mg, lot # 4293A, comparing it with the reference product, Tenex^R Tablets, 2 mg, lot # 0940758, has been found **incomplete** by the Division of Bioequivalence due to the Deficiencies # 1 cited above.

2. The in-vitro dissolution testing conducted by Amide Pharmaceutical on its Guanfacine HCl Tablets, 2 mg and 1 mg, has been found **acceptable**.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following current specifications:

Not less than (b)4 - the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the Recommendations and Deficiencies.

/S/ 11/17/96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 11/24/96

Concu /S/ 10/17/95 Date: _____

Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-673 (original, duplicate), HFD-630(OGD), HFD-600(Hare), HFD-652(Huang, Nguyen), HFD-344(CViswanathan), Drug File, Division File

HNguyen/11-03-95/WP #74673sdw.795

Attachments: 1 page

NP # 74673 sdw. 795 Attachment

AMIDE PHARMACEUTICAL, INC.

GUANFACINE TABLETS

FORMULATION COMPARISION FOR GUANFACINE TABLETS

EACH TABLET CONTAINS	GUANFACINE TABLETS 2 mg mg/tablet	1 mg mg/tablet
Guanfacine Hydrochloride (Equivalent to 2 mg and 1 mg Guanfacine)	2.346 *	1.173
Lactose Anhydrous, NF	(b)4 -	(b)4 - Confidential Business
Microcrystalline Cellulose,	(b)4 -	
D&C Yellow #10 Aluminum Lake	(b)4 -	
Starch Pregelatinized, NF		
Magnesium Stearate, NF		
Talc, USP		
TOTAL WEIGHT:	125.00	125.0

* Contains 2% excess to compensate for moisture content and production losses.

NOTE: Bioequivalence study is performed on 2 mg strength only.